40. (New) The soluble fusion protein of Claim 38, wherein said non-toxin protein sequence comprises a poly-histidine tract.

41. (New) The soluble fusion protein of Claim 38, wherein said fusion protein is substantially endotoxin-free.

REMARKS

Applicants appreciate the removal of the rejections under 35 U.S.C. 103 and 35 U.S.C. 112, second paragraph. Claims 10-14 and 25-31 were at issue and have been rejected by the Examiner in the present Application. In particular, Claims 10-14 and 25-31 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly being non-enabled. Applicants believe the present amendments and following remarks traverse the Examiner's rejections of the Claims.

I. Claims 10-14 and 25-31 Are Fully Enabled

The Examiner rejected Claims 10-14 and 25-31 under 35 U.S.C. §112, first paragraph, as allegedly being non-enabled. In particular, the Examiner states that "[o]ne of skill in the art would be forced into undue experimentation to identify all portions of a single antigen which can be produced as a soluble and neutralizing vaccine, given that the art teaches of the unpredictability of using a single antigen for vaccination it would be an undue burden and be unpredictable to use the broadly claimed soluble and neutralizing portions for vaccination." (Office Action, pg 3-4). Applicants disagree with both the Examiner's characterization of the art, and the need for undue experimentation to identify portions of a protein which would yield a neutralizing vaccine.

The Examiner cites Ellis, R.W. (Chpt. 29, "Vaccines" [Plotkin, S.A, et al, (ed), published by W.B. Saunders Co. (Philadelphia), 1988, pg 571, 2nd full paragraph], in support of the proposition that "[i]t is well recognized in the art that it is unclear whether a single protein derived from a pathogen will elicit protective immunity." Applicants respectfully disagree with this characterization of this reference and submit that the Examiner has presented the quote from page 571 completely out of context. In fact, Ellis describes using recombinant DNA technology to prepare a large quantity of a **single protein**, such that this

protein can be used as a vaccine (Ellis gives the example of Hepatitis B surface antigen[1]). As such, Applicants submit that this reference is in direct contrast to the Examiner's contention that 'it is unclear whether a single protein ... will elicit protective immunity'.

The Examiner goes on to argue that one of skill in the art would be forced into undue experimentation to identify all portions of a single antigen which can be produced as a soluble and neutralizing vaccine. In other words, the Examiner argues that it would require undue experimentation to identify every portion of *C. botulinum* toxin types B, E, and A, which could generate a neutralizing vaccine. Applicants traverse this rejection, and submit that the Claims are fully enabled because the antigenic proteins (toxins) are already identified (a 'key' factor according to Ellis) and one skilled in the art could readily determine which portions of these toxin are neutralizing.

The specification provides ample guidance in determining which portions of these toxins would produce neutralizing vaccine. In particular, detailed *in vivo* assays used to determine the neutralizing ability of antibodies to the three toxins in question are provided in the Specification [Toxin A - Example 23 (pgs 178-184), Toxin B - Example 36 (pgs 229-230), and Toxin E - Example 42 (pgs 247-248)]. Each of these Examples demonstrates testing a portion (*e.g.* C fragment) of the given toxin (A, B, or E) using a mouse model which "is the art accepted method for detection of botulinal toxins in body fluids and for the evaluation of anti-botulinal antibodies". (Specification, pg 181, lines 16-17). As such, if any experimentation were needed to determine other portions of these toxins (besides the receptor binding domain specifically detailed in the Examples), the law permits it; "[t]he key word is 'undue' not 'experimentation'. *In re Angstadt and Griffin*, 190 USPQ 214, 219 (CCPA, 1976). Indeed, "a considerable amount of experimentation is permissible ... if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... ". *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. App., 1982). *In re Wands*, 8 USPQ 2d 1400, 1404 (CAFC 1988). Applicants submit, therefore, that the instant Specification provides ample guidance as to the direction in which any required experimentation should proceed as the Examples described above teach

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[1] Ellis, pg 571, 3rd full paragraph.

how to determine if any given portion for Toxins A, B, and E will generate neutralizing antibodies. As such, the Claims as they stand are enabled, and this rejection should be withdrawn.

II. Claims 32-41 Have Been Added

Applicants also note that Claims 32-41 have been added. These Claims differ in that they recite "at least a portion of the receptor binding domain of one or more *Clostridial botulinum* toxins ...[2]". (*See e.g.* Claim 32). As such, these Claims are also clearly enabled as they further specify that at least a portion of the receptor binding domain (*i.e.* the C fragment) be part of the fusion protein, and the Specification describes neutralization assays to determine neutralizing portions (*See*, Examples 23, 36, and 42, describing *in vivo* neutralizing assays for portion of Toxins A, B, and E, respectively). Consequently, Claims 32-41 should also be allowed.

CONCLUSION

Applicants submit that, with due consideration of all the factors discussed above, the patentability of the Claims is evident. For the foregoing reasons, it is submitted that the Examiner's rejection the Claims was erroneous, and reversal of this rejection is respectfully requested. If the Examiner should wish to discuss the grounds for rejection, he may contact the undersigned by collect call at 617-252-3353.

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Peter G. Carroll
Registration No. 32,837

MEDLEN & CARROLL, LLP
220 Montgomery Street, Suite 2200
San Francisco, California 94104

[2] Support for the neutralizing ability of antibodies generated to the C fragment of these toxins is found in the Specification (Toxin A, pg 181, line 10 - pg 183, line 23, Toxin B, pg 229, line 22 - pg 230, line 8, and Toxin E, pg 247, line 16 - pg 248, line 3).